Fecal Calprotectin Testing
Clinical Coverage Criteria

Description

Fecal calprotectin testing is used in practice to differentiate inflammatory bowel disease (IBD) from irritable bowel syndrome (IBS) where the signs and symptoms are very similar, but the pathology is different. IBD is characterized by inflammation of the gastrointestinal tract, whereas IBS is characterized by abnormalities in gut motility. In the differential diagnosis of IBD versus IBS, the purpose of fecal calprotectin testing is to inform the decision whether to proceed to endoscopy with biopsy in order to confirm a diagnosis of IBD, either Crohn's disease or ulcerative colitis. A fecal calprotectin level of less than 50 µg/g is suggestive of a low likelihood of IBD, and allows the avoidance of unnecessary diagnostic interventions, such as colonoscopy.

Policy

This Policy applies to the following Fallon Health products:

☒ Fallon Medicare Plus, Fallon Medicare Plus Central (Medicare Advantage)

☒ MassHealth ACO

☒ NaviCare HMO SNP (Dual Eligible Medicare Advantage and MassHealth)

☒ NaviCare SCO (MassHealth-only)

☒ PACE (Summit Eldercare PACE, Fallon Health Weinberg PACE)

☒ Community Care (Commercial/Exchange)

Prior authorization is not required for fecal calprotectin testing (CPT 83993) effective for dates of service on or after January 1, 2023. Refer to Coding section below for ICD-10-CM codes that will support medical necessity.

Fallon Health Clinical Coverage Criteria

Fallon Health Clinical Coverage Criteria apply to all products.

Fecal calprotectin testing is considered medically necessary when the outcome of the test will be used to inform the decision of whether to proceed to endoscopy with biopsy, in order to confirm a diagnosis of Inflammatory Bowel Disease (IBD), either ulcerative colitis or Crohn's disease (suspected inflammatory bowel disease).

The evidence on clinical validity (sensitivity, specificity, negative predictive value) permits inference on clinical usefulness as a result of avoidance of endoscopy with biopsy in patients who are unlikely to have an inflammatory disease. In most cases, a negative calprotectin rules out IBD, thereby sparing most people with irritable bowel syndrome (IBS) from having to have invasive investigations, such as colonoscopy (Waugh et al., 2013).

Medicare Variation

None.

Medicare statutes and regulations do not have coverage criteria for fecal calprotectin testing. Medicare does not have an NCD for fecal calprotectin testing. National Government Services, Inc. is the Part A/B Medicare Administrative Contractor (MAC) with jurisdiction in our service area. National Government Services, Inc. does not have an LCD for fecal calprotectin testing (Medicare Coverage Database search 03/25/2025). Coverage criteria are not fully established in Medicare

statutes, regulations, NCDs or LCDs, therefore, Fallon Health Clinical Coverage Criteria are applicable.

MassHealth Variation

MassHealth does not have Guidelines for Medical Necessity Determination fecal calprotectin testing, therefore, Fallon Health Clinical Coverage Criteria are applicable (MassHealth website search 03/25/2025).

Exclusions

- Fecal calprotectin testing is considered experimental/investigational in the management of inflammatory bowel disease (IBD), including the management of active inflammatory bowel disease and surveillance for relapse of disease in remission.
    - The clinical utility of fecal calprotectin testing has not been established for monitoring active IBD (Monitoring Active IBD).
    - There is a need for high-quality RCTs to determine whether monitoring fecal calprotectin in patients who are in remission can reduce relapse rates and improve the quality of life (QOL) for patients with IBD (Prediction of Relapse with IBD in Remission).

Summary of Evidence

Inflammatory Bowel Disease

Inflammatory bowel disease (IBD) is an umbrella term used to describe disorders that cause chronic inflammation of the gastrointestinal tract. Symptoms include diarrhea, as well as abdominal pain, nausea, fever, loss of appetite, fatigue and at times rectal bleeding. The two most common forms of IBD are Crohn's disease and ulcerative colitis. Both Crohn's disease and ulcerative colitis are remitting and relapsing conditions with a variable course of progression. There is currently no cure for IBD. Therapeutic approaches to treat these diseases mainly focus on achieving and prolonging remission. Most current strategies, which target control of symptoms, do not appear to significantly alter the natural course of the disease, although reductions in the need for surgery or the occurrence of neoplasia have been reported in some Crohn's disease and ulcerative colitis population-based cohorts over time (Peyrin-Biroulet et al., 2015).

The incidence of IBD peaks at approximately age 15–29 years, and 10%–15% of new diagnoses occur among adults aged ≥60 years. A recent study, funded by the Centers for Disease Control and Prevention (CDC), estimates the incidence, prevalence, and racial-ethnic distribution of physician-diagnosed IBD in the United States using health insurance claims data. The INPUT (INcidence, Prevalence, Treatment, and OUTcomes in Patients with IBD) study found that the prevalence of IBD was 721 cases per 100,000 people (95% CI, 717-726). Extrapolated to the 2020 United States Census, an estimated 2.39 million Americans are diagnosed with IBD. Of note, the study revealed significant variation by race. The prevalence of IBD per 100,000 population was 812 (95% CI, 802-823) in White, 504 (95% CI, 482-526) in Black, 403 (95% CI, 373-433) in Asian, and 458 (95% CI, 440-476) in Hispanic Americans. According to the study team, it remains uncertain whether this difference is due to biased diagnosis or underlying biological variances, therefore, more research is needed to understand the reasons for these racial and ethnic differences in IBD prevalence (Lewis et al., 2023).

The CDC also examined Medicare claims data to determine the prevalence of IBD in the older population. In 2018, 0.40% and 0.64% of 25.1 million Medicare fee-for-service beneficiaries aged ≥ 67 years had a diagnosis of Crohn's disease or ulcerative colitis, respectively. During 2001−2018, the age-adjusted prevalence of both diseases increased: Crohn's disease annual percentage change (APC) = 3.4%, ulcerative colitis APC = 2.8%. The increase was higher among non-Hispanic Black persons: Crohn's disease APC = 5.0%, ulcerative colitis APC = 3.5%, than it was among non-Hispanic White, Hispanic, and Asian/Pacific Islander persons (Xu et al., 2021).

Irritable Bowel Syndrome

Irritable bowel syndrome (IBS) is a chronic, often debilitating, and highly prevalent disorder of gut-brain interaction (previously called a functional gastrointestinal disorder). In clinical practice, IBS

is characterized by symptoms of recurrent abdominal pain and diarrhea. The Rome IV criteria, derived by consensus from a multinational group of experts in the field of disorders of gut-brain interaction, can be used to diagnose IBS for both clinical and research purposes. The prevalence of IBS is approximately 4.4%–4.8% in the United States and affects most commonly women and individuals younger than 50 years. Symptoms of IBS can greatly affect patients' quality of life. IBS causes a significant burden to health care systems worldwide. High levels of health care resource utilization, testing that is often unnecessary or performed too frequently, and significant regional variation in testing and treatment further contribute to substantial direct and indirect costs. The high prevalence of IBS greatly influences IBS patient care. Colonoscopy is a common test used to confirm the absence of pathology that might be responsible for a patient's intestinal symptoms, such as IBD, microscopic colitis, or colon cancer. This test imposes a significant burden to the patient and direct financial costs. This impact is further heightened because many primary care providers directly request a colonoscopy before GI consultation. Colonoscopy is one of the most frequent and most expensive tests used during the evaluation of IBS symptoms. Evidence to support performing a colonoscopy in younger patients without 'alarm features' is poor. In the absence of alarm features, there seems to be no justification for colonoscopy in subjects with IBS younger than 45 years. In patients older than 45 years, a recent negative colonoscopy for colon cancer screening or for other investigative purposes should mitigate the need for another colonoscopy for IBS symptoms in the absence of new alarm features. Either fecal calprotectin or fecal lactoferrin and C-reactive protein be checked in patients without alarm features and with suspected IBS and diarrhea symptoms to rule out IBD. Strong recommendation; moderate quality of evidence for C-reactive protein and fecal calprotectin. Strong recommendation; very low quality of evidence for fecal lactoferrin. (Lacy et al., 2021).

Fecal Calprotectin Testing to Diagnose Suspected Inflammatory Bowel Disease

Calprotectin is a calcium- and zinc-binding protein of the S-100 protein family which is mainly found within neutrophils and throughout the human body. The presence of fecal calprotectin is a consequence of neutrophil migration into the gastrointestinal tissue due to an inflammatory process. Fecal calprotectin concentrations demonstrate good correlation with intestinal inflammation. Although fecal calprotectin is a sensitive marker for inflammation in the gastrointestinal tract, it is not a specific marker for IBD. Increased levels of fecal calprotectin are also seen in gastrointestinal malignancies, infections, polyps and with the use of nonsteroidal anti-inflammatory drugs. The interpretation of the concentration should thus always consider the clinical history of the patient, their symptomatology, and factors that could affect the results. Several fecal calprotectin tests are available in the United States, including fully quantitative laboratory-based technologies. Enzyme-linked immunosorbent assay (ELISA) has been used for many years and is gradually being replaced by newer techniques such as fluorescence, chemiluminescence and immunoturbidimetry. Almost all techniques recommend 50 µg/g as the cutoff for the normal concentration for adults and children older than 4 years. Owing to the absence of standardization, assays are not interchangeable. Thus, patients must be monitored using the same method to limit interassay variation, which could lead to misinterpretation.

Ileocolonoscopy with biopsy is considered the gold standard for the diagnosis of IBD. In recent years, many studies have been conducted to find a suitable laboratory marker with sufficient sensitivity and specificity for the purpose of differentiating IBD and IBS. The purpose of fecal calprotectin testing is to inform the decision whether to proceed to endoscopy with biopsy in order to confirm a diagnosis of IBD, either ulcerative colitis or Crohn's disease. A fecal calprotectin level of less than 50 µg/g is suggestive of a low likelihood of IBD.

Distinguishing between Crohn's disease and ulcerative colitis is of importance in evaluating patients with clinical presentation suspicious for IBD due to differences in prognosis and therapeutic interventions.

Randomized Controlled Trials

A test is clinically useful if the results inform management decisions that improve the net health outcome of care. Direct evidence of clinical utility is provided by studies that compare health outcomes for patients managed with and without the test. Because these are intervention studies,

the preferred evidence would be from randomized controlled trials (RCTs). No RCTs were identified that assessed the use of fecal calprotectin testing to diagnose suspected IBD. Indirect evidence on clinical utility rests on clinical validity. If the evidence is insufficient to demonstrate test performance, no inferences can be made about clinical utility. Indirect evidence supports the clinical usefulness of fecal calprotectin in patients with suspected IBD for whom endoscopy is being considered. The evidence on clinical validity (sensitivity, specificity, negative predictive value) permits inference on clinical usefulness as a result of avoidance of endoscopy with biopsy in patients who are unlikely to have an inflammatory disease.

Systematic Reviews and Meta-Analyses
Several systematic reviews and meta-analyses evaluating the accuracy of fecal calprotectin testing for distinguishing between IBD and IBS or IBD and non-IBD have been conducted.

In 2013, Waugh et al in the U.K. published a meta-analysis of studies evaluating the accuracy of fecal calprotectin testing for distinguishing between IBD and non-IBD. The inclusion criteria were studies comparing FC as a guide to inflammation of the lower intestine, ideally with histology as the reference test, in newly presenting patients. Exclusion criteria included studies of FC for monitoring activity of IBD or response to treatment in people with known IBD. Twenty-eight studies were deemed eligible and were included in the quantitative synthesis. Studies were pooled when there were a minimum of 4 using the same calprotectin cutoff. A pooled analysis of 5 studies (n=596 patients) using fecal calprotectin detected by ELISA to differentiate between IBD and IBS in adults at a cutoff of 50 µg/g had a combined sensitivity of 0.93 (95% confidence interval [CI], 0.83 to 0.97) and a combined specificity of 0.94 (95% CI, 0.73 to 0.99). In these 5 studies the negative predictive value (NPV) ranged from 73% to 100% in adults with IBS or IBD. A pooled analysis of 6 studies (n=1100) using fecal calprotectin to differentiate between IBD and non-IBD in adults and children (5 of the 6 studies included only children, most of whom had been referred to pediatric gastroenterologists) had a combined sensitivity of 0.99 (95% CI, 0.95 to 1.00) and a combined specificity of 0.74 (95% CI, 0.59 to 0.86). In these 6 studies, the NPV ranged from 93% to 100%. The authors conclude that calprotectin testing is a reliable method for differentiating between inflammatory and noninflammatory disease of the bowel, although there are inevitably trade-offs between sensitivity and specificity, with some false positives (IBS with positive calprotectin). In most cases, a negative calprotectin rules out IBD, thereby sparing most people with IBS from having to have invasive investigations, such as colonoscopy. Areas of uncertainty include the optimum management of people with borderline results (50–150 µg/g), most of whom do not have IBD. Some interesting findings emerged:

- Raising the cut-off to 100 µg/g would have little effect (4%) on sensitivity but much more (14%) on specificity. The NPV hardly changes (98% vs. 97%) but the PPV improves from 28% to 49%.
- Raising the cut-off to 150 µg/g gives NPV 97% and PPV 71%.
- Considerable savings could result, although the authors note that a considerable number of those with calprotectin levels of < 50 µg/g were still referred (reasons not given) and underwent endoscopy (reasons not given), and so they suggest that repeat calprotectin testing of people with levels of < 150 µg/g should be considered.

Henderson et al., 2014, conducted a systematic review and meta-analysis of studies that reported fecal calprotectin levels before the endoscopic investigation of IBD in patients less than 18 years old. Eight studies met inclusion criteria (six prospective and two retrospective case-control studies); methodological quality was determined in detail for each study. The 8 studies presented fecal calprotectin levels at presentation in 715 patients, 394 pediatric IBD patients, and 321 non-IBD controls. In six studies, the cut-off value was 50 µg/g, whereas in two studies, the cut-off was 100 µg/g. The pooled sensitivity and specificity for the diagnostic utility of fecal calprotectin during the investigation of suspected pediatric IBD were 0.978 (95% CI, 0.947-0.996) and 0.682 (95% CI, 0.502-0.863), respectively. Fecal calprotectin had a high sensitivity and a modest specificity during the diagnosis of suspected pediatric IBD in this analysis.

Petryszyn et al., 2019 conducted a meta-analysis that evaluated the efficacy of fecal calprotectin as a diagnostic marker of IBD in patients with symptoms suggestive for IBD. The analysis included 19 studies (15 prospective and 4 retrospective; published through December 2018) with

5,032 patients. Patients were over 16 years of age and had gastrointestinal symptoms, chronic diarrhea, or any other reason that may raise IBD suspicion. In the majority of included studies the diagnostic fecal calprotectin cutoff value was 50 µg/g (n=14). An IBD diagnosis was confirmed in 620 (12.3%) patients, with prevalence ranging from 2.7% to 68.1%. Calculated pooled sensitivity and specificity were 0.882 [95% confidence interval (CI), 0.827-0.921] and 0.799 (95% CI, 0.693-0.875), respectively. There was a higher sensitivity of fecal calprotectin among studies with an IBD prevalence ≤ 30% as compared to among studies with a prevalence > 30% (0.902 [95% CI, 0.856 to 0.935] versus 0.825 [95% CI, 0.661 to 0.920]; p=0.041). Regarding risk of bias, the overall methodological quality of included studies was deemed to be "good;" however, 11 studies included some 6 patients that were not representative of those who would receive the fecal calprotectin test in clinical practice and selection bias may have existed in 5 studies. The authors concluded that out of 100 hypothetical cases with an IBD prevalence of 12.3%, 18 non-disease patients would have a colonoscopy performed and 1 patient with IBD would not be referred for a colonoscopy. Additionally, it was determined that incorporating a fecal calprotectin test into the regular diagnostic work-up would reduce the need for colonoscopy by 66.7%.

Shi et al (2022) conducted an umbrella review to summarize the evidence from published systematic reviews and meta-analyses (including Waugh et al., 2013 and Petryszyn et al., 2019 discussed above), evaluating the performance of non-invasive tests, including fecal calprotectin, for IBD in various clinical conditions and age groups, Performance and test validity were classified into 3 clinical scenarios: diagnosis, activity assessment, and prediction of recurrence. In total, 106 assessments from 43 studies were included with 17 non-invasive tests. For diagnosis, in distinguishing IBD from non-IBD in a mixed population, at a cut-off of 50 µg/g, fecal calprotectin had a pooled sensitivity of 0.850 (95% CI, 0.605 to 0.955) and specificity of 0.847 (95% CI, 0.647 to 0.943). At a cutoff of 100 µg/g, fecal calprotectin had a sensitivity of 0.72 (95% CI, 0.63 to 0.80) and specificity of 0.82 (95% CI, 0.78 to 0.86). ANCA showed the highest specificity 0.971 (95% CI, 0.964–0.977). The specificity of fecal lactoferrin in distinguishing IBD from non-IBD in a mixed population was 0.95 (95% CI, 0.88-0.98). For diagnosis, in distinguishing IBD from IBS in a mixed population, fecal calprotectin was again the most sensitive test. At a cutoff of 50 µg/g, fecal calprotectin had a sensitivity of 0.97 (95% CI, 0.91 to 0.99) and specificity of 0.76 (95% CI, 0.66 to 0.84). At a cutoff of 100 µg/g, fecal calprotectin had a sensitivity of 0.92 (95% CI, 0.85 to 0.96) and specificity of 0.86 (95% CI, 0.82 to 0.89). For specificity, fecal lactoferrin performed the best in distinguishing IBD from IBS: 0.94 (95% CI, 0.91–0.96). The performance of fecal calprotectin in patients with Crohn’s disease [sensitivity: 0.95 (95% CI, 0.92-0.97; specificity: 0.84 (95% CI, 0.80-0.87)] was better than in patients with ulcerative colitis [sensitivity: 0.78 (95% CI, 0.69-0.86; specificity: 0.78 (95% CI, 0.70-0.84)].

Evidence-Based Practice Guidelines
The American College of Gastroenterology (ACG) published guidelines on the Management of Crohn’s Disease in Adults (Lichtenstein et al., 2018). The College gave a strong recommendation based on a moderate level of evidence that fecal calprotectin is a helpful test that should be considered to differentiate the presence of inflammatory bowel disease from irritable bowel syndrome.

Evidence-Based Consensus
A 2021 AGA Clinical Practice Update on Management of Inflammatory Bowel Disease in Elderly Patients, states: Fecal calprotectin or lactoferrin may help prioritize patients with a low probability of IBD for endoscopic evaluation. Individuals presenting with hematochezia or chronic diarrhea with intermediate to high suspicion for underlying IBD, microscopic colitis, or colorectal neoplasia should undergo colonoscopy (Ananthakrishnan et al., 2021).

Monitoring Disease Activity in Inflammatory Bowel Disease
For individuals who have been diagnosed with IBD, fecal calprotectin testing could allow clinicians to monitor disease activity and guide therapeutic decision-making as an alternative to endoscopy.

Crohn’s disease

The goal of treatment in Crohn's disease is to induce and maintain remission (symptomatic and endoscopic remission) while avoiding long-term use of corticosteroids and immunomodulators, which are associated with increased risk of side effects. Not surprisingly, patients identify clinical symptoms as the most important target to treat. In STRIDE II, clinical response in an immediate target. For Crohn's disease, clinical response is defined as a decrease of at least 50% in PRO2 (abdominal pain and stool frequency). Clinical remission is an intermediate target.

Clinical symptoms are poorly correlated with degree of mucosal inflammation in Crohn's disease, and it is not infrequent to discover significant mucosal inflammation during complete clinical remission. It is widely accepted that treating to the target of endoscopic healing is associated with improved long-term outcomes and may reduce the risk of bowel damage. Mucosal inflammation, even in the presence of clinical remission, is associated with long-term disease-related complications, flares, and surgeries. Endoscopic healing was selected as the primary treatment target in the original STRIDE consensus and also scored the highest in STRIDE II as a long-term target. Accordingly, most clinicians in STRIDE II, considered clinical response and then clinical remission as the most important immediate and intermediate treatment goals in Crohn's disease. In voting, clinical response is an immediate treatment target, scored the highest of all recommendations, with a mean score of 9.0 on a scale of 1-10 where "10" demotes complete agreement and "1" complete disagreement (STRIDE II, Turner et al., 2021).

There is a lack of consistency in defining thresholds for endoscopic response and remission. In the systematic review, the following definitions prevailed: for endoscopic response, a >50% decrease in the SES-CD (simple endoscopic score in CD) or CDEIS (endoscopic index of severity) and for endoscopic remission SES-CD ≤ 2 points or CDEIS<3 and lack of ulcerations (i.e., any ulcerations). Taken together, clinical remission should be considered as a mandatory intermediate target but in addition, objective improvement in measures of inflammation must subsequently be shown, because clinical symptoms are poorly correlated with degree of mucosal inflammation in Crohn's disease, and it is not infrequent to discover significant mucosal inflammation during complete clinical remission.

Ulcerative Colitis

Ulcerative colitis is a chronic inflammatory bowel disease with peak onset in early adulthood. Untreated, the natural history of the disease is one of relapsing and remitting mucosal inflammation. The severity of UC is generally classified as mild-to-moderate or moderate-to-severe. Based on population-based cohort studies, the majority of patients with ulcerative colitis have a mild to moderate course, generally most active at diagnosis and then in varying periods of remission or mild activity. The mainstay of treatment for mild-moderate ulcerative colitis is the 5-ASA class of medications, including sulfasalazine, mesalamine, and diazo-bonded 5-ASA (Ko et al., 2019). There are a number of different drug classes for long-term management of moderate to severe ulcerative colitis, including tumor necrosis factor (TNF)-α antagonists, anti-integrin agent (vedolizumab), Janus kinase inhibitor (tofacitinib) and immunomodulators (thiopurines, methotrexate). In general, most drugs that are initiated for induction of remission are continued as maintenance therapy, if they are effective (Feuerstein et al., 2020).

The American College of Gastroenterology suggests treating patients with Ulcerative Colitis to achieve mucosal healing (defined as resolution of inflammatory changes (Mayo Endoscopic Subscore (MES) 0 or 1) to increase the likelihood of sustained steroid-free remission and prevent hospitalizations and surgery (conditional recommendation, low quality of evidence) (Rubin et al., 2019). Unlike in Crohn's disease, clinical symptoms are well correlated with endoscopic degree of inflammation in Ulcerative Colitis. Normal stool frequency and absence of rectal bleeding are the main clinical targets in patients with Ulcerative Colitis. The absence of diarrhea and blood is an independent predictor of relapse-free survival, colectomy-free survival, and long-term outcomes. In STRIDE II, clinical response in an immediate target. For Ulcerative Colitis, clinical response is defined as a decrease of at least 50% in PRO2 (abdominal pain and stool frequency). Clinical remission is an intermediate target.

In STRIDE, endoscopic healing was a long-term target in Ulcerative Colitis. The STRIDE II systematic review did not identify new evidence to change this recommendation. Several

endoscopic scores have been explored in Ulcerative Colitis, but the Mayo Endoscopic Score (MES) and Ulcerative Colitis Endoscopic Index of Severity are the most studied. Endoscopic healing is commonly defined as MES <1, but complete endoscopic healing (i.e., MES 0) is associated with superior disease outcomes.

The correlation of serum and fecal inflammatory biomarkers with clinical disease activity, endoscopic, and histological indices has been described in children and in adults with Ulcerative Colitis. The American College of Gastroenterology suggests fecal calprotectin as a surrogate for endoscopy when endoscopy is not feasible or available to assess for mucosal healing (conditional recommendation, very low quality of evidence) (Rubin et al., 2019).

Randomized Controlled Trials
One RCT (Colombel et al., 2018) using fecal calprotectin testing along with other measures to manage treatment in patients with IBD on maintenance therapy was identified.

The CALM trial was a multicenter, open label, randomized controlled trial (NCT01235689) that compared endoscopic outcomes in patients with moderate to severe Crohn's disease whose treatment was managed based on tight control including fecal calprotectin ≥250 µg/g and CRP >5 mg/L, Crohn's Disease Activity Index (CDAI), and prednisone use vs CDAI response and prednisone use (clinical management). Treatment was escalated according to pre-specified criteria. A total of 244 patients were randomized 1:1 to the tight control group (n=122) or clinical management (n=122) Mean disease duration in the tight control group was 1.0 years; mean disease duration in the clinical management group was 0.9 years. Twenty-nine (29) (24%) patients in the clinical management group and 32 (26%) patients in the tight control group discontinued the study, mostly because of adverse events. The primary endpoint was mucosal healing with an absence of deep ulcers on ileocolonoscopy at 48 weeks after randomization. A significantly higher proportion of patients in the tight control group achieved the primary endpoint at week 48 [56 (46%) of 122 patients] compared to the clinical management group [37 (30%) of 122 patients], with a Cochran-Mantel-Haenszel test-adjusted risk difference of 16.1% (95% CI 3·9-28·3; p=0.010).

The CALM trial demonstrated that patients whose treatment was escalated based on biomarkers, symptoms, and prednisone use achieved improved clinical and endoscopic outcomes compared with those whose treatment was escalated based on symptoms and prednisone use alone. However, the relationship between biomarker cutoff levels and mucosal improvements was not fully established. The CALM trial did not test whether using fecal calprotectin, as decision criteria for treatment changes, improved the capability to achieve tight control. Although a post hoc analysis found that, in the tight control group, fecal calprotectin levels frequently influenced the decision to escalate treatment, the contribution of fecal calprotectin to the tight control cannot be determined from this study design.

Reinisch et al., 2020, conducted a post hoc analysis of CALM to identify drivers of treatment escalation and evaluate the association between biomarker cutoff concentrations and endoscopic end points. The proportion of patients achieving the primary end point in CALM and endoscopic response were evaluated according to the biomarker cutoffs used in the study. The proportion of patients achieving Crohn's Disease Endoscopic Index of Severity (CDEIS) <4 and no deep ulcers 48 weeks after randomization was evaluated according to CRP < 5 mg/L or ≥ 5 mg/L and FC < 250 µg/g or ≥ 250 µg/g. The post hoc analysis found that the proportion of patients who achieved the primary end point CDEIS <4 and no deep ulcers was significantly greater for those with FC < 250 µg/g (74%; P < 0.001), with an additive effect for CRP < 5 mg/L. Fecal calprotectin < 250 µg/g, CRP < 5 mg/L, and CDAI < 150 gave a sensitivity and specificity of 72% and 63%, respectively, and positive and negative predictive values of 86% and 42%, respectively, for CDEIS <4 and no deep ulcers 48 weeks after randomization.

The post hoc analysis of CALM demonstrated that a cutoff of FC <250 µg/g is a useful surrogate marker for mucosal healing in Crohn's Disease. However, the post hoc analysis was limited by the design of the CALM study, in which actual values of fecal calprotectin levels above 250 µg/g were not captured and were only classified as >250 µg/g. Therefore, fecal calprotectin levels were quantitated only when they were ≤250 µg/g, and no optimal fecal calprotectin cutoff using

receiver operating characteristic analysis could be determined. Furthermore, because escalation decisions were made throughout the trial using the 250 µg/g cutoff, it could not be determined whether more patients would have met the primary end point if a lower cutoff was used. Although exploration of cutoff levels for fecal calprotectin to indicate mucosal healing was not the original objective of the CALM study, the results of this post hoc analysis of CALM support the cutoff proposed by earlier studies, as few patients with FC > 250 µg/g at week 48 achieved the primary end point, and 79% of patients with baseline FC ≥ 250 µg/g achieved the primary end point if FC was <250 µg/g and CRP <5 mg/L 48 weeks after randomization (Reinisch et al., 2020).

Cohort Studies

Sipponen et al., 2008, evaluated the clinical significance of fecal calprotectin and fecal lactoferrin in the assessment of endoscopic activity in Crohn's disease. A total of 77 patients underwent one or more ileocolonoscopies (n=106) with scoring of Crohn's disease index of severity (CDEIS). Patients provided stool samples for calprotectin and lactoferrin measurements and blood samples for CRP. Both fecal calprotectin and lactoferrin correlated significantly with CDEIS (Spearman's r 0.729 and 0.773, p < 0.001). With a cutoff level of 200 µg/g for fecal calprotectin concentration, sensitivity was 70%, specificity 92%, positive predictive value (PPV) 94%, and negative predictive value (NPV) 61% in predicting endoscopically active disease (CDEIS >/= 3). A fecal lactoferrin concentration of 10 µg/g as the cutoff value gave a sensitivity, specificity, PPV, and NPV of 66%, 92%, 94%, and 59%. Sensitivity of CDAI >/= 150 to detect endoscopically active disease was only 27%, specificity 94%, PPV 91%, and NPV 40%. CRP > 5 mg/l gave a sensitivity, specificity, PPV, and NPV of 48%, 91%, 91%, and 48%.

D'Haens et al., 2012 examined how reliably fecal calprotectin levels reflect mucosal disease activity. In total, 126 IBD patients underwent colonoscopy and experienced endoscopists recorded the Simple Endoscopic Score for Crohn's Disease (SES-CD) and the Crohn's Disease Endoscopic Index of Severity (CDEIS) in Crohn's disease (CD) patients and the Mayo Endoscopic Score in ulcerative colitis patients. The median (interquartile range [IQR]) fecal calprotectin levels were 175 (44-938) µg/g in Crohn's disease and 465 (61-1128) µg/g in ulcerative. Correlations were significant with endoscopic disease scores in both Crohn's disease and in ulcerative. Using ROC statistics, a cutoff value of 250 µg/g indicated the presence of large ulcers with a sensitivity of 60.4% and a specificity of 79.5% (PPV 78.4%, NPV 62.0%) in Crohn's disease. Levels ≤ 250 µg/g predicted endoscopic remission (CDEIS ≤ 3) with 94.1% sensitivity and 62.2% specificity (PPV 48.5%, NPV 96.6%). In ulcerative colitis, a fecal calprotectin > 250 µg/g gave a sensitivity of 71.0% and a specificity of 100.0% (PPV 100.0%, NPV 47.1%) for active mucosal disease activity (Mayo > 0). Calprotectin levels significantly correlated with symptom scores in ulcerative colitis (r = 0.561, p < 0.001), but not in Crohn's disease.

Schoepfer et al., 2010 evaluated the correlation between the Simple Endoscopic Score for Crohn's disease (SES-CD) with fecal calprotectin, CRP, blood leukocytes, and the CDAI in Crohn's disease patients undergoing ileocolonoscopy. SES-CD was defined as follows: inactive 0-3; mild 4-10; moderate 11-19; and high > or =20. During the study period, 18 patients underwent Ileocolonoscopy twice, therefore 140 endoscopies were performed in 122 patients. Indications for endoscopy were clinically active disease (flare) (n = 76, 54%), assessment of endoscopic activity after medical treatment (n=45, 32%), dysplasia surveillance for long-standing disease (n=15, 11%), and stricture dilation (n=4,3%). The SES-CD correlated significantly with levels of fecal calprotectin (Spearman's rank correlation coefficient r = 0.75), CRP (r = 0.53), blood leukocytes (r = 0.42), and the CDAI (r = 0.38). For all items a p < 0.01 was found. Calprotectin was the only biomarker able to discriminate the four subgroups of SES-CD (104+/-138 vs. 231+/-244 µg/g, p < 0.001 for discriminating inactive from mild disease, 231+/-244 vs. 395+/-256 µg/g, p = 0.008 for discriminating mild from moderate, and 395 ± 256 vs. 718 ± 320 µg/g, p < 0.001 for discriminating moderate from high endoscopic activity). Calprotectin (cutoff 50 µg/g) was elevated in 11 out of 26 (42%) of patients with inactive disease compared with 101 out of 114 (89%) with active disease. In patients with mild activity, elevated calprotectin was found in 32 out of 40 (80 %) of patients compared with 24 out of 27 (89 %) of patients with moderate and 45 out of 47 (96 %) with severe disease activity. Calprotectin with a cutoff of ≥ 70 µg/g had the

best overall accuracy (87%) for the detection of endoscopically active disease, followed by calprotectin with the ≥ 50 µg/g cutoff (accuracy 84%).

Lobatón et al., 2013, evaluated the ability of a new quantitative point of care test (QPOCT) to predict endoscopic remission. Fecal calprotectin was determined simultaneously by an enzyme-linked immunoassay test (FC-ELISA) and a FC-QPOCT in CD patients undergoing colonoscopy. Clinical disease activity was assessed according to the Crohn's Disease Activity Index (CDAI). Endoscopic results were assessed according to the Crohn's Disease Endoscopic Activity Index of Severity (CDEIS) and postoperative recurrence according to the Rutgeerts' score. Pearson's correlation between FC-ELISA and FC- QPOCT was 0.879 ($p < 0.001$).The prediction of endoscopic remission (CDEIS<3), using FC-QPOCT (cut-off 272 µg/g) and FC-ELISA (cut-off 274 µg/g) presented an AUC of 0.933 and 0.935 respectively. For prediction of CDEIS <3, a 274 µg/g cut-off value of FC-ELISA gave a sensitivity of 77%, a specificity of 97%, a NPV of 75%, and a PPV of 98% (global accuracy 85%). A 272 µg/g cut-off value FC-QPOCT gave a sensitivity of 79%, a specificity of 97%, a NPV of 76%, and a PPV of 98% (global accuracy 86%). The prediction of complete endoscopic remission defined as CDEIS=0 with FC-QPOCT and FC-ELISA presented an area under the curve (AUC) of 0.831 and 0.801 respectively. A 200 µg/g cut-off value of FC-QPOCT had a sensitivity of 75% and a specificity of 77%. A 261.8 µg/g cut-off value of FC-ELISA had a sensitivity of 75% and a specificity of 76%. All patients with ulcers (n = 68) had a fecal calprotectin level of > 250 µg/g with both techniques, and 13 out of 42 patients with no ulcers had a fecal calprotectin level of > 250 µg/g.

Systematic Reviews and Meta-Analyses

A systematic review by Mosli et al., 2015 evaluated the sensitivity and specificity of fecal calprotectin, fecal lactoferrin and C-reactive protein in adults and some children with previously diagnosed ulcerative colitis or Crohn's disease to detect endoscopically confirmed active disease, After removal of duplicates, 2,516 studies were screened for inclusion. Of these, 29 studies were judged to be potentially relevant and underwent a full text review. Nineteen studies with 1069 ulcerative colitis patients and 1033 Crohn's disease patients met eligibility criteria. In the individual studies, multiple cut-off points were identified for fecal calprotectin, ranging from 6 to 280 µg/g. Pooled sensitivity and specificity estimates for fecal calprotectin were 0.88 (95% CI 0.84–0.90) and 0.73 (95% CI 0.66–0.79), respectively. The pooled sensitivity and specificity for Crohn’s disease were 0.87 (95% CI 0.82–0.91) and 0.67 (95% CI 0.58–0.75), respectively. When the diagnostic accuracy of fecal calprotectin was assessed by disease type, the point estimate for specificity was higher in ulcerative colitis 0.79 (95% CI: 0.68–0.87) compared with Crohn’s disease 0.67 (95% CI: 0.58–0.75). Fecal calprotectin was determined to be a highly sensitive marker of endoscopically active IBD, especially ulcerative colitis, with a cut-off point of 50 µg/g. An important finding of this review is that the existing literature regarding biomarkers is highly diverse. Only a minority of the publications identified met the search criteria, which specified evaluation of symptomatic patients with endoscopy as a gold standard. The authors speculate that this issue is responsible for much of the controversy that currently exists regarding the value of biomarkers in IBD management. The fecal calprotectin cut-off point of 50 µg/g that was identified as optimal for the detection of endoscopically active disease in symptomatic patients is substantially different from the value of 250 µ g/g reported by Lin et al., 2014 in patients whose disease was in symptomatic remission. It is notable that fecal calprotectin showed better specificity in UC, whereas the sensitivity was similar in the two diseases (pooled sensitivity=0.88 (95% CI 0.84–0.92) and specificity=0.79 (95% CI 0.68–0.87) compared with CD (pooled sensitivity=0.87 (95% CI 0.82–0.91) and specificity=0.68 (95% CI 0.58–0. 75). The relatively poor specificity of fecal calprotectin in Crohn’s disease is a concern, as a false positive test could lead to treatment of a patient without endoscopically active disease.

Rokkas et al., 2018 conducted a systematic review and meta-analysis to determine the diagnostic performance of fecal calprotectin in assessing IBD activity in adults. In total, 25 studies were eligible with 2,822 IBD patients and 298 control patients. Fecal calprotectin in IBD (Crohn's disease and ulcerative colitis) showed a pooled sensitivity of 85% (95% CI, 82–87%) and a specificity of 75% (95% CI, 71–79%) for diagnosing active disease. The sub-group analysis revealed that FC performed better in UC than in CD (pooled sensitivity 87.3% vs 82.4%,

specificity 77.1% vs 72.1% and AUC 0.91 vs 0.84). In order to examine fecal calprotectin accuracy performance at different cutoff values, the authors carried out subgroup analyses taking into account three cut off levels, up to 50 µg /g (7 studies), up to 100 mcg/gr (20 studies) and > 100 µg /g (29 studies). For the cut off level of 50 µg/g the relevant pooled results were; sensitivity (95% CI) = 90.6% (87.9-92.9), specificity = 60.7% (53.7-67.4) and AUC 0.91. The respective values for cut off levels up to 100 µg /g and > 100 µg /g were 88.2 % (86.5– 89.8), 67 % (63.3 – 70.6), 0.89 and 80 % (77.7-82.2), 78.2% (75.7-80.6), 0.86, respectively. These pooled results clearly showed that as the cutoff value increases, sensitivity falls, and specificity increases. Examining the optimum FC cut-off levels, the best sensitivity (90.6%) was achieved at 50 µg/g, whereas the best specificity (78.2%) was found at levels >100 µg/g. The modest specificity of fecal calprotectin in Crohn's disease, i.e. 72.1%, is potentially a problem, since the remaining 27.9% are false positive tests and could lead to treating patients with inactive disease. Other studies have stressed this issue in the literature.

The umbrella review by Shi et al., 2022, discussed previously in the section on suspected IBD, also reported the diagnostic performance of fecal calprotectin in monitoring disease activity. This review, which included the systematic reviews by Mosli et al. and Rokkas et al. summarized above, found that among the tests evaluated in assessing IBD activity in a mixed population, fecal calprotectin with a cutoff of 50 µg/g performed the best, with a sensitivity of 0.92 (95% CI, 0.90 to 0.94). The specificity of fecal calprotectin was 0.60 (95% CI, 0.52-0.67). At a cut-off of 100 µg/g the sensitivity and specificity of fecal calprotectin in a mixed population were 0.84 (95% CI, 0.80-0.88) and 0.66 (95% CI, 0.0.59-0.73); at a cut-off of 250 µg/g, the sensitivity and specificity were 0.80 (95% CI, 0.76-0.84) and 0.66 (95% CI, 0.59-0.73). However, ultrasound and magnetic resonance enterography (MRE) performed better, with comparable sensitivity and higher specificity. MRE had the highest specificity 93% (95% CI, 90%-95%). The specificity of ultrasound was 0.883 (95% CI, 0.581-0.976).

- For Crohn's disease, in assessing disease activity, ultrasound showed the best specificity at 0.977 (0.700–0.999), and contrast-enhanced ultrasound (CEUS) was the most sensitive test with a sensitivity of 0.94 (0.87–0.97). At a cut-off of 50 µg/g, the sensitivity and specificity of fecal calprotectin for assessing disease activity in Crohn's disease were 0.831 (95% CI, 0.740-0.895) and 0.502 (95% CI, 0.359-0.644). At a cut-off of 100 µg/g, the sensitivity and specificity were 0.725 (95% CI, 0.657-0.784) and 0.0.728 (95% CI, 0.622-0.814). At a cut-off of 200 µg/g, the sensitivity and specificity were 0.495 (95% CI, 0.361-0.629) and 0.882 (95% CI, 0.738-0.952). The sensitivity and specificity of fecal lactoferrin were 0.82 (95% CI, 0.73-0.88) and 0.71 (95% CI, 0.63-0.78).
- For Ulcerative Colitis, in assessing disease activity, fecal calprotectin had a sensitivity of 0.873 (95% CI, 0.854-0.891) and a specificity of 0.771 (95% CI, 0.737-0.803) with endoscopic activity as a reference. With histology as a reference, fecal calprotectin performed slightly worse. Ultrasound had a sensitivity of 0.866 (95% CI, 0.800-0.939) and a specificity of 0.819 (95% CI, 0.456-0.961).

Evidence-Based Practice Guidelines

The American College of Gastroenterology (ACG) published guidelines on the Management of Crohn's Disease in Adults (Lichtenstein et al., 2018). In a Summary Statement the College finds that fecal calprotectin and fecal lactoferrin measurements may have an adjunctive role in monitoring disease activity.

The goals of therapy in IBD have historically been based on symptomatic response with good control of symptoms and improved quality of life. We now have objective measures of inflammation that may allow tighter control of the inflammatory process. Monitoring of the inflammatory response includes fecal markers, serum markers, imaging studies, and endoscopic assessment. The concept of "treating to target" is using the assessment of response of both clinical and inflammatory parameters to define remission. What is not clear is whether this rigorous definition of remission will lead to long-term improvement of outcomes or modify the disease course. With the advances that have been made in the medical therapy of Crohn's disease, the concept of treating to target is becoming more realistic but there is still a need to have long-term observational studies to see whether complete clinical and inflammatory

remission is required in all patients. The presence of biomarkers of disease activity can be but should not exclusively serve as end point for treatment as normalization of the biomarker can occur despite having active mucosal inflammation or ulceration (Lichtenstein et al., 2018).

A summary statement without recommendation from the American College of Gastroenterology indicated that fecal calprotectin and fecal lactoferrin measurements may have an adjunctive role in monitoring disease activity. The goals of therapy in IBD have historically been based on symptomatic response with good control of symptoms and improved quality of life. We now have objective measures of inflammation that may allow tighter control of the inflammatory process. Monitoring of the inflammatory response includes fecal markers, serum markers, imaging studies, and endoscopic assessment. The concept of “treating to target” is using the assessment of response of both clinical and inflammatory parameters to define remission. What is not clear is whether this rigorous definition of remission will lead to long-term improvement of outcomes or modify the disease course. With the advances that have been made in the medical therapy of CD, the concept of treating to target is becoming more realistic but there is still a need to have long-term observational studies to see whether complete clinical and inflammatory remission is required in all patients. The presence of biomarkers of disease activity can be but should not exclusively serve as end point for treatment as normalization of the biomarker can occur despite having active mucosal inflammation/ulceration (Lichtenstein et al., 2018).

In 2018, the American Gastroenterological Association (AGA) published a Clinical Practice Update Expert Review on the diagnosis and management of functional gastrointestinal symptoms in patients with IBD (Colombel et al., 2019), The AGA recommends a stepwise approach to rule-out ongoing inflammatory activity in IBD patients that includes fecal calprotectin, endoscopy with biopsy, and imaging. In those patients with indeterminate fecal calprotectin levels and mild symptoms, clinicians may consider serial calprotectin monitoring at three to six month intervals to facilitate anticipatory management. However, "the optimal cutoff for biomarkers remains a source of debate" and overtreatment for symptoms that are due to functional pathophysiology rather than inflammation can increase adverse effects with no symptomatic benefit.”

A 2023 guideline from the AGA on the role of biomarkers for the management of ulcerative colitis made seven conditional recommendations.

- In patients with ulcerative colitis in symptomatic remission, the panel suggests the use of a monitoring strategy that combines biomarkers and symptoms, rather than symptoms alone (Moderate Certainty of Evidence).
- In patients with ulcerative colitis in symptomatic remission, the panel suggests using fecal calprotectin <150 µg/g, normal fecal lactoferrin, and/or normal CRP to rule out active inflammation and avoid routine endoscopic assessment of disease (Low Certainty of Evidence).
- In patients in symptomatic remission but elevated biomarkers, and in patients with moderate to severe symptoms with normal biomarkers (fecal calprotectin >150 mg/g, elevated fecal lactoferrin, elevated CRP), the panel suggests endoscopic assessment of disease rather than empiric treatment adjustment (Very Low Certainly of Evidence).
- In patients with ulcerative colitis with moderate to severe symptoms, suggestive of flare, the panel suggests using fecal calprotectin >150 µg/g, elevated fecal lactoferrin, or elevated CRP to inform treatment decisions and avoid routine endoscopic assessment of disease (Low Certainty of Evidence).
- In patients with ulcerative colitis with mild symptoms, with elevated stool or serum markers of inflammation (fecal calprotectin >150mg/g, elevated fecal lactoferrin, or elevated CRP), the panel suggests endoscopic assessment of disease activity to inform treatment decisions (Very Low Certainty of Evidence).
- In patients with ulcerative colitis with mild symptoms, with normal stool or serum markers of inflammation (fecal calprotectin < 150mg/g, normal fecal lactoferrin, or normal CRP), the panel suggests endoscopic assessment of disease activity to inform treatment decisions (Very Low Certainty of Evidence).

- In patients with ulcerative colitis, the panel makes no recommendation in favor of, or against, a biomarker-based monitoring strategy over an endoscopy-based monitoring strategy to improve long-term outcomes (Knowledge Gap).

Evidence-Based Consensus
The concept of the treat-to-target approach, which was first put forward by the Selecting Therapeutic Targets in Inflammatory Bowel Disease (STRIDE) consensus in 2015, aims to achieve disease remission by adjusting therapy according to the achievement of treatment targets (Peyrin-Biroulet et al., 2015). STRIDE has shifted the goal of IBD treatment from symptomatic control to support targeting objective therapeutic endpoints to prevent long-term disease complications. In 2021, STRIDE was updated, encompassing evidence- and consensus-based recommendations for treat-to-target strategies (STRIDE II recommendations, Turner et al., 2021).

STRIDE II recommends considering changing treatment if normalization of CRP (to values under the upper limit of normal) and fecal calprotectin (to 100–250 µg/g) have not been achieved. Fecal calprotectin has high sensitivity and lower specificity in identifying mucosal inflammation, CRP has the opposite characteristics: it has higher specificity but low sensitivity. There is a footnote stating that the cutoff value of fecal calprotectin is dependent on the desired outcome. “Lower thresholds have been proposed for reflecting deep healing (both endoscopic and transmural healing) or histological healing, whereas higher values reflect less stringent outcomes.” The STRIDE II systematic review supported using a fecal calprotectin cutoff value of 150 µg/g to identify endoscopic healing. However, given the low reliability of fecal calprotectin, the range of 100 to 250 µg/g is considered a gray zone, whereas even values < 600 µg/g can still be associated with minimal inflammation.

Prediction of Relapse for IBD in Remission
Calprotectin has been used to predict relapse in individuals with IBD who are in remission. A marker to predict relapse could improve the net health outcome if preemptive treatment were found to eliminate recurrences or reduce their severity.

Randomized Controlled Trials
One unblinded RCT (Lasson et al., 2015) evaluated whether pharmacological intervention guided by fecal calprotectin prolongs remission in patients with ulcerative colitis. Analysis of fecal calprotectin was performed monthly for 18 months. A fecal calprotectin value of 300 µg/g was set as the cut-off for intervention, which was a dose escalation of the oral 5-aminosalicylate (5-ASA) agent. The primary study end-point was the number of patients to have relapsed by month 18. There were relapses in 18 out of 51 patients (35.3%) in the intervention group and 20 out of 40 (50.0%) in the control group had experienced at least one relapse by month 18 ($p = 0.23$), For 10 of the 18 patients (55.6%) with a relapse in the intervention group, the calprotectin level did not reach the cut-off value before they relapsed. In 28 out of 51 patients (54,9%), fecal calprotectin levels increased to > 300 µg/g in at least one of the monthly samples, In the control group, 28 out of 40 (70%) of patients had at least one calprotectin value > 300 µg/g. Eight out of 28 patients (28.6%) with active intervention relapsed, whereas 16 out of 28 patients (57.1%) in the control group with a calprotectin concentration >300 mg/g experienced a relapse ($p < 0.05$). Active intervention significantly reduced relapse rates, although no significant difference was reached between the groups overall..

Cohort Studies
Kallel et al., 2010 prospectively evaluated the role of fecal calprotectin as a predictive marker of relapse in Crohn’s disease patients in clinical remission. A total of 53 patients in clinical remission were followed for 12 months. During that time, 10 (18.9%) developed clinical relapse. The median fecal calprotectin was significantly higher in the relapsed patients compared to non-relapsed patients (380.5 vs 155 µg/g, $p<0.001$). With a cut-off of 340 µg/g, fecal calprotectin had a sensitivity and specificity of 80% and 90.7 %, respectively, in predicting clinical relapse.

Ferreiro-Iglesias et al., 2016, conducted a prospective observational study to evaluate the predictive value of a rapid fecal calprotectin test to predict flares in patients with IBD under

maintenance therapy with infliximab. Fecal calprotectin was measured using a rapid test on a stool sample obtained within 24 hours before infliximab infusion. Clinical examination was performed two months after that infusion. Fifty-three patients were included (52.8% female). Thirty-three patients (62.3%) had Crohn's disease and 20 (37.7%) had ulcerative colitis. All patients were in remission at inclusion. After two months, 41 patients (77.4%) remained in clinical remission and 12 (22.6%) presented a relapse. Fecal calprotectin (mean ± SD) in relapsing and non-relapsing disease was 332 ± 168 and 110 ± 163 µg/g, respectively ($p<0.005$). A fecal calprotectin concentration >160 µg/g had a sensitivity of 91.7%, and specificity of 82.9% to predict relapse.

Systematic Reviews and Meta-Analyses

Heida et al., 2017 conducted a systematic review to determine the accuracy of fecal calprotectin monitoring in asymptomatic patients, Six studies met the review inclusion criteria and evaluated fecal calprotectin levels every one to three months. One-third of patients had a relapse during the study period, although the definitions of relapse varied across studies. Five of the six studies used an upward trend of fecal calprotectin between two measurements as the threshold. Asymptomatic patients with IBD who had fecal calprotectin levels above the study's cutoff had a 53% to 83% probability of developing disease relapse within the next 2 to 3 months, while patients with normal fecal calprotectin levels had a 67% to 94% probability of remaining in remission in the next 2 to 3 months. Calprotectin levels began to rise two to three months before clinical relapse. The investigators could not identify the best fecal calprotectin cutoff for monitoring purposes.

The umbrella review by Shi et al., 2022, discussed previously in the sections on suspected IBD and monitoring disease activity in IBD, also reported the performance of fecal calprotectin in assessing disease recurrence. For recurrence in IBD, the only test was fecal calprotectin. The sensitivity was 0.78 (95% CI, 0.72-0.83) and the specificity was 0.73 (95% CI, 0.68-0.77). For recurrence in CD, the overall sensitivity of fecal calprotectin was 0.75 (95% CI, 0.64-0.84) and the specificity was 0.71 (95% CI, 0.64-0.76). For postoperative CD recurrence, small intestine contrast ultrasonography (SICUS) had the highest sensitivity (0.99 (95% CI, 0.99–1.00) and fecal calprotectin had the highest specificity for postoperative CD clinical recurrence (0.88 (95% CI, 0.80–0.93), while fecal calprotectin for endoscopic recurrence had higher sensitivity (0.82 (95% CI, 0.73-0.89). The sensitivity of postoperative fecal calprotectin for prediction of recurrence in CD at a cut-off of 50 µg/g was 0.90 (95% CI, 0.83-0.96) and the specificity was 0.36 (95% CI, 0.25-0.47). While the sensitivity of postoperative fecal calprotectin for prediction of recurrence in CD at a cut-off of 200 µg/g was 0.55 (95% CI, 0.43-0.69) and the specificity was 0.71 (95% CI, 0.62-0.79). Postoperative MRI had high sensitivity (0.973 (95% CI, 0.891–0.998) and specificity (0.837 (95% CI, 0.616–0.959)) as did the various subtypes of postoperative ultrasound. For recurrence in UC, the sensitivity of fecal calprotectin was 0.75 (95% CI, 0.70-0.79) and the specificity was 0.77 (95% CI, 0.74-0.80).

Shi et al., 2023, conducted a meta-analysis to evaluate the diagnostic accuracy of fecal calprotectin for predicting relapse in IBD. A total of 24 studies (n=2260) were included in the analysis. All studies used a prospective study design and enrolled patients with quiescent IBD at baseline. Seven of 24 studies solely involved Crohn's disease patients; 7 studies solely involved ulcerative colitis patients, and 10 studies included both Crohn's disease and ulcerative colitis patients. Fecal calprotectin was measured at baseline. IBD relapse was identified with clinical symptoms and or endoscopic findings on follow-up over a period of time. Cut-off values for predicting relapse ranged from 50 to 500 µg/g, but most of them were mainly in the range of 100 to 250 µg/g. Overall, the quality of the included studies was good. Blinding of reference standard results was reported in all but one study. The pooled sensitivity and specificity of fecal calprotectin for predicting relapse in IBD was 0.720 (0.528 to 0.856) and 0.740 (0.618 to 0.834), respectively. An optimal fecal calprotectin cut-off value for predicting IBD relapse of 152 µg/g was identified.

Evidence-Based Practice Guidelines

In 2018, the American Gastroenterological Association (AGA) published a guideline on Functional Gastrointestinal Symptoms in Patients with Inflammatory Bowel Disease (Colombel et al., 2019.

The AGA recommends a stepwise approach to rule-out ongoing inflammatory activity in IBD patients that includes fecal calprotectin, endoscopy with biopsy, and imaging. In those patients with indeterminate fecal calprotectin levels and mild symptoms, clinicians may consider serial calprotectin monitoring at three to six month intervals to facilitate anticipatory management. However, "the optimal cutoff for biomarkers remains a source of debate" and overtreatment for symptoms that are due to functional pathophysiology rather than inflammation can increase adverse effects with no symptomatic benefit.

Analysis of Evidence (Rationale for Determination)

No RCTs were identified that assessed the use of fecal calprotectin testing to diagnose suspected IBD. Several systematic reviews and meta-analyses evaluating the accuracy of fecal calprotectin testing for distinguishing between IBD and IBS or IBD and non-IBD have been published. Evidence from an umbrella review suggests that fecal calprotectin is the most sensitive noninvasive test in distinguishing IBD from non-IBD and IBD from IBS at a cut-off of 50 µg/g. Indirect evidence supports the clinical usefulness of fecal calprotectin in patients with suspected IBD for whom endoscopy is being considered. The evidence on clinical validity (sensitivity, specificity, NPV) permits inference on clinical usefulness as a result of avoidance of endoscopy with biopsy in patients who are unlikely to have an inflammatory disease. In most cases, a negative fecal calprotectin rules out IBD, thereby sparing most people with IBS from having to have invasive investigations, such as colonoscopy.

Studies using fecal calprotectin to manage IBD have not used consistent cutoff values. One RCT using fecal calprotectin testing along with other measures to monitor disease activity in patients with IBD on maintenance therapy was identified. This study demonstrated improved endoscopic outcomes when treatment was escalated based on cutoffs for inflammatory biomarkers, fecal calprotectin, C-reactive protein, and CD Activity Index (CDAI) remission vs CDAI response alone. This RCT did not test whether using fecal calprotectin as decision criteria for treatment changes improved outcomes. A post hoc analysis found that fecal calprotectin levels frequently influenced the decision to escalate treatment, The post hoc analysis demonstrated that a cutoff of FC < 250 µg/g is a useful surrogate marker for mucosal healing in Crohn’s disease. However, the post hoc analysis was limited by the design of the study, in which actual values of fecal calprotectin levels above 250 µg/g were not captured and were only classified as > 250 µg/g. Therefore, fecal calprotectin levels were quantitated only when they were ≤ 250 µg/g, and no optimal fecal calprotectin cutoff using receiver operating characteristic analysis could be determined.

Furthermore, because escalation decisions were made throughout the trial using the 250 µg/g cutoff, it could not be determined whether more patients would have met the primary end point if a lower cutoff was used. Systematic reviews recommended different cut-off points to manage disease activity (50 µg/g, 150 µg/g and 250 µg/g). Fecal calprotectin levels in the normal range (< 50 µg/g) or significantly elevated fecal calprotectin values (> 250 µg/g) can reliably be interpreted as remission or active disease. However, fecal calprotectin values in the “intermediate or gray zone” ranging from 100 to 250 µg/g are difficult to classify. Fecal calprotectin as a single marker seems therefore insufficient to provide an accurate prediction of mucosal inflammation in all IBD patients. Evidence from an umbrella review suggests that for assessing disease activity in IBD, magnetic resonance imaging enterography (MRE) (sensitivity 0.83 (95% CI, 0.75-0.89), specificity 0.93 (95% CI, 0.90-0.95) and ultrasound (sensitivity 0.964 (95% CI, 0.761-0.927), specificity 0.883 (95% CI, 0.591-0.976) performed well.

Calprotectin has been used to predict relapse in individuals with IBD who are in remission. A marker to predict relapse could improve the net health outcome if preemptive treatment were found to eliminate recurrences or reduce their severity. Evidence from an umbrella review suggests that that biomarkers perform well in diagnosis, while radiological examinations, especially MRE and US, were more prominent in assessing activity and predicting recurrence. Fecal calprotectin levels correlate with the disease activity of inflammatory bowel diseases, however, the utility of fecal calprotectin in predicting IBD relapse remains to be determined.

Coding

The following codes are included below for informational purposes only; inclusion of a code does not constitute or imply coverage or reimbursement.

CPT Codes

CPT Code	Code Description
83993	Calprotectin, fecal

ICD-10 CM Diagnosis Codes

When medical necessity criteria are met, the following ICD-10-CM Diagnosis Codes will support medical necessity. For outpatient claims, providers report the ICD-10-CM code for the diagnosis shown to be chiefly responsible for the outpatient services in the first-listed or primary diagnosis position.

10-CM diagnosis codes	Code Description
K52.3	Indeterminate colitis
K59.00	Constipation, unspecified
K59.01	Slow transit constipation
K59.02	Outlet dysfunction constipation
K59.04	Chronic idiopathic constipation
K59.09	Other constipation
K59.1	Functional diarrhea
K90.9	Intestinal malabsorption, unspecified
R10.0	Acute abdomen
R10.10	Upper abdominal pain, unspecified
R10.11	Right upper quadrant pain
R10.12	Left upper quadrant pain
R10.30	Lower abdominal pain, unspecified
R10.31	Right lower quadrant pain
R10.32	Left lower quadrant pain
R10.33	Periumbilical pain
R10.84	Generalized abdominal pain
R63.4	Abnormal weight loss
R10.9	Unspecified abdominal pain
R11.0	Nausea
R11.2	Nausea with vomiting, unspecified
R14.0	Abdominal distension (gaseous)
R14.1	Gas pain
R14.3	Flatulence
R19.4	Change in bowel habit
R19.5	Other fecal abnormalities
R19.7	Diarrhea, unspecified
R19.8	Other specified symptoms and signs involving the digestive system and abdomen

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Policy history

Origination date:	01/01/2023
Review/Approval Dates:	Technology Assessment Committee: 07/26/2022 (policy origination), 02/27/2024 (annual review, criteria unchanged, added new sections: Summary of Evidence and Analysis of Evidence (Rationale for Determination), updated references), 03/25/2025 (annual review; added Medicare Variation and MassHealth Variation sections; no changes to coverage criteria). Utilization Management Committee: 04/15/2025 (annual review; approved).

Instructions for Use

Fallon Health complies with CMS's national coverage determinations (NCDs), local coverage determinations (LCDs) of Medicare Contractors with jurisdiction for claims in the Plan's service area, and applicable Medicare statutes and regulations when making medical necessity determinations for Medicare Advantage members. When coverage criteria are not fully established in applicable Medicare statutes, regulations, NCDs or LCDs, Fallon Health may create internal coverage criteria under specific circumstances described at § 422.101(b)(6)(i) and (ii).

Fallon Health generally follows Medical Necessity Guidelines published by MassHealth when making medical necessity determinations for MassHealth members. In the absence of Medical Necessity Guidelines published by MassHealth, Fallon Health may create clinical coverage criteria in accordance with the definition of Medical Necessity in 130 CMR 450.204.

For plan members enrolled in NaviCare, Fallon Health first follow's CMS's national coverage determinations (NCDs), local coverage determinations (LCDs) of Medicare Contractors with jurisdiction for claims in the Plan's service area, and applicable Medicare statutes and regulations when making medical necessity determinations. When coverage criteria are not fully established in applicable Medicare statutes, regulations, NCDs or LCDs, or if the NaviCare member does not meet coverage criteria in applicable Medicare statutes, regulations, NCDs or LCDs, Fallon Health then follows Medical Necessity Guidelines published by MassHealth when making necessity determinations for NaviCare members.

Each PACE plan member is assigned to an Interdisciplinary Team. PACE provides participants with all the care and services covered by Medicare and Medicaid, as authorized by the interdisciplinary team, as well as additional medically necessary care and services not covered by Medicare and Medicaid. With the exception of emergency care and out-of-area urgently needed care, all care and services provided to PACE plan members must be authorized by the interdisciplinary team.

Not all services mentioned in this policy are covered for all products or employer groups. Coverage is based upon the terms of a member's particular benefit plan which may contain its own specific provisions for coverage and exclusions regardless of medical necessity. Please consult the product's Evidence of Coverage for exclusions or other benefit limitations applicable to this service or supply. If there is any discrepancy between this policy and a member's benefit plan, the provisions of the benefit plan will govern. However, applicable state mandates take precedence with respect to fully-insured plans and self-funded non-ERISA (e.g., government, school boards, church) plans. Unless otherwise specifically excluded, federal mandates will apply to all plans.